UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,665	11/17/2003	Mark Selby	PP01635.007	5235

27476 7590 01/13/2006

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,665	SELBY ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-37,42-45,66-69,77 and 79-88* is/are pending in the application.

4a) Of the above claim(s) *80-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-37,42-45,66-69, 77, 79, 85-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 34-37, 42-45, 66-69, 77, 79-88 are pending in the application.

2. In the prior action, mailed on July 29, 2005, claims 1-78 were pending, with claims 1-33, 38-41, 46-65, 70-76, and 78 withdrawn as to non-elected inventions; and claims 34-37, 42-45, 66-69, and 77 rejected. In the amendment of October 31, 2005, the Applicant cancelled claims 1-33, 38-41, 46-65, 70-76, and 78; amended claims 34, 37, 42, 45, 66, and 69; and added new claims 79-88.

3. Newly added claims 80-82 and 83 and 84 correspond, respectively, to the previously restricted Groups VI and V. Thus, these claims are therefore withdrawn from consideration.

4. Currently, claims 34-37, 42-45, 66-69, 77, 79, and 85-88 are pending and under consideration.

Specification

5. **(Prior Objection- Withdrawn)** The disclosure was objected to because of the following informalities: the specification indicated on page 5 that the E2 coding sequence in Figure 4 (SEQ ID NO: 6) begins at base 1997, but later indicates that the E2 protein sequence begins at residue 384 of the HCV polyprotein (page 22), which corresponds to base 2067 of SEQ ID NO: 6. In view of the amendment of the application to correct the description of Figure 4, the objection is withdrawn.

Claim Rejections - 35 USC § 101 and 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **(Prior Rejection- Withdrawn)** Claims 34, 35, 37, 42, 45, 66, 67, and 69 were rejected under 35 U.S.C. 101, and under 35 U.S.C. 112, first paragraph, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for nucleic acids encoding any protein with up to about 20% variation from any HCV E2 protein fragment corresponding to residues 384-661 of HCV-1, without regard for the polypeptides ability to induce an immune response against HCV. In view of the amendment of these claims, the rejection is withdrawn.

8. **(New Rejection- Necessitated by Amendment)** Claims 34, 35, 37, 42, 43, 45, 66, 67, 69, 77, 79, and 85-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims have been amended, or drafted, to read on nucleic acids, or compositions comprising such, encoding a polypeptide having at least about 80% identity to an HCV sequence, and which is able to induce an anti-HCV immune response.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present case, the application refers to analogs of HCV sequences that are able to induce an anti-HCV response. Pages 9-10. However, each of these embodiments of the claimed invention comprises an actual HCV sequence. See e.g., Figures 3 and 4. There is no description in the application of any non-HCV sequence that is capable of inducing an anti-HCV immune response, or any identification of any structure that would capable of inducing such a response. Nor do the claims require that the claimed polypeptides retain an epitope from the corresponding HCV sequence. It is noted that the claims require the presence of a sequence with at least 80% identity to residues 384-661 of an HCV sequence, but do not require the retention of any epitopes from that sequence. Thus, the claims read on polypeptides comprising a polypeptide of 277 amino acids, 55 of which may vary from the corresponding HCV sequence. I.e., approximately 1 in 5 amino acids may vary from the HCV sequence. It is further noted that epitopes, regions against which immune responses are induced, span between 5 and 12 amino acids in length (depending on the epitope, and the type of immune response). See e.g., U.S.

2005/0272097, page 8 paragraph [0117] (teaching the length of antibody epitopes is about 5-6 residues); and U.S. 2005/0220858, page 3 paragraph [0023], and Green et al. (Eur J Immunol 34: 2510-19) at 2510 (each teaching that T-cell epitopes are generally between 8-12 residues in length). Thus, polypeptides in which one in five residues may be altered include embodiments wherein there is no conserved epitope in the sequence.

Further, the art teaches that the results on a particular protein modification is uncertain without specific teachings as to the association of the modified residue and the protein structure or function, and that modification of a single residue may result in a change in the immunogenic profile of a protein. See e.g. Bowie et al., Science 247: 1306-10 at 1306 (teaching uncertainty in the result of protein modification generally); and Riffkin et al., Gene 167: 279-83 (teaching that a single residue change results in antigenically different proteins). Thus, the teachings in the art indicate that there is uncertainty in the art regarding what polypeptides falling with the scope of the structural limitations of the claim would meet the functional requirements. The art indicates that the 80% homology limitation is not a structural characteristic that corresponds to the presence of the required function (as would be the case where an epitope is shared with an HCV polypeptide). In view of the lack of such correlation, and the uncertainty as to which species of with the genus of sequences with 80% homology to an HCV sequence would meet the functional requirement, the application has not provided sufficient information to demonstrate possession of the claimed genus. The claims are therefore rejected as lacking sufficient written description support.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. **(Prior Rejection- Withdrawn)** Claims 37, 45, and 69 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it was unclear whether the Applicant intended the term "immunogenic" as a descriptor for the nucleic acid sequence itself, or the protein sequence encoded by the claimed nucleic acid. In view of the amendments to the claims, the rejection is withdrawn.

11. **(New Rejection- Necessitated by Amendment)** Claims 77 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 77 was previously presented. This claim read on a cell line that comprises a first HBsAg and a chimeric antigen, wherein the chimeric antigen comprises a second HBsAg linked to a an HCV immunogenic polypeptide. The application teaches than HCV polypeptides are derived from the HCV polyprotein. Thus, previously, the claim appeared to read on an immunogenic polypeptide that was derived from, and therefore comprised an amino acid sequence of, an HCV isolate.

However, claim 79 has now been added to the application. This claim depends from claim 77, and purports to narrow the claim to embodiments wherein the HCV polypeptide has at least about 80% identity to an HCV sequence, and is capable of inducing an immune response against HCV, but does not require the presence of an actual HCV sequence. Claims 85-88 have similar language. In view of the addition of new claims 79 and 85-88, it is not clear what the extent of the term "an HCV immunogenic polypeptide" is.

12. **(New Rejection- Necessitated by Amendment)** Claim 87 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on the vector of claim 85 "wherein the substantially complete S domain is covalently attached at its amino terminus to the immunogenic polypeptide." The claim is rejected because there are two substantially complete S domains in claim 85, and while it appears that the claim intends to refer to the S domain present in the fusion protein, claim 87 does not clearly state as such. It is therefore unclear which of the complete S domains in claim 85 is being referred to in claim 87. Clarification of the claim language is required.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. **(Prior Rejection- Maintained)** Claims 34-36, 42-44, and 66-68 were rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Major et al. (J Virol 69: 5798-5805- of record in the Nov. 2003 IDS) in view of Michalak et al., (J Gen Virol 78: 2299-2306), and further in view of Valenzuela et al. (Bio/Technology 3: 323-26- also of record in the Nov. 2003 IDS). The Applicant traverses this rejection on the basis of an assertion that the Major reference teaches away from the use of HCV E2 proteins for an anti-HCV vaccine. This argument is not found persuasive.

The Applicant refers to teachings in Major noting the variability in the HCV envelope regions, and a statement in the Major reference that indicates this variability "bring into question the suitability of these antigens in immunization programs." However, the reference does not indicate that fusions of the HBsAg and E2 would be unable to induce anti-HCV immune responses. Further, the reference indicates that while the variability indicates that a vaccine comprising the sequence may not be effective against heterologous strains of HCV, the art has demonstrates "successful immunization against homologous HCV strains." Page 5804, left column. Thus, the teachings in Major indicate that fusions comprising E2 may only have limited operability, but do not, overall, indicate that those in the art would have had no motivation for the construction of such fusion proteins.

Further, the later teachings of the Michalak indicate that fragments of the HCV E2 protein comprising residues 384-661 "is the best candidate for a soluble form" of HCV to mimic E2 in viral particulars, and that such E2 particles may be useful either in serodiagnosis or in subunit vaccines. Thus, this reference both supports the indications referred to by Major that the E2 antigens would be effective in inducing anti-HCV responses, and indicates that even if such proteins would not be useful in vaccines, raising an immune response against the antigen would still be beneficial for other purposes, such as serodiagnosis. The Applicant's arguments regarding the teachings of Major are therefore not found persuasive.

The Applicant additionally asserts that the number of references relied on by the Examiner is evidence of the non-obviousness of the claims. In response to this argument, it is noted that reliance on a large number of references in a rejection does not, without more, weigh

against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). This argument is therefore also not found persuasive.

For these reasons, and the reasons of record, the rejection is maintained.

15. **(Prior Rejection- Maintained)** Claim 77 was rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs et al. (U.S. 6,306,625), in view of Major, Michalak, and Valenzuela as applied to claims 34-36, 42-44, and 66-68 above. The Applicant traverses this rejection on the basis that Jacobs does not teach or suggest the fusion of HBsAg with an HCV antigen. This argument is not found persuasive in view of the inclusion of the Major and Michalak references in the statement of the rejection, and for the reasons indicated above with respect to claims 34-36, 42-44, and 66-68. Further, the rejection is extended to new claim 79.

16. **(Prior Rejection- Maintained)** Claim 37 was rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs in view of Major, Michalak, and Valenzuela as applied to claim 77 above, and further in view of the teachings of and GenBank Accession Numbers X02763, and M62321. The Applicant traverses the rejection based on the assertion that the cited art provides no motivation to combine an HBsAg sequence with an HCV E2 sequence. In view of the inclusion of the teachings of the Major and Michalak references as described previously and above, and for the same reasons as indicated with respect to the teachings of Major and Michalak in the rejection of claims 34-36, 42-44, and 66-68 above, this assertion is not found persuasive. The rejection is therefore maintained.

17. **(Prior Rejection- Withdrawn)** Claims 45 and 69 were rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs in view of the teachings of Major, Michalak, Valenzuela, and GenBank Accessions M62321 and X02763 as applied to claim 37 above (cumulatively, Jacobs etc.), and further in view of Selby et al. (U.S. 6,096,505), Chapman et al. (Nuc Acids Res 19: 3979-86), and Hartikka et al. (Hum Gene Ther 7: 1205-17). These claims are drawn to vectors comprising the sequence of SEQ ID NO: 6, or sequences with at least 80% identity thereto, and immunogenic compositions comprising such. SEQ ID NO: 6 is disclosed in the application as coding the claimed fusion protein. Page 5, description of Figure 4. The application indicates that the vector is a modified (by insertion of the coding sequence for the fusion protein) form of the pCMVII plasmid. The claim depends in part on the teachings of the Selby et al. reference, U.S. 6,096,505, In traversal of the rejection, the Applicant states that the "claimed invention" and the Selby patent were commonly owned, or subject to obligation of assignment to the same person, at the time of invention, and that the current application and the Selby patent are commonly assigned. Response, page 18 (first full paragraph). The rejection is therefore withdrawn.

18. **(New Rejection- Necessitated by Amendment)** New claims 85-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs in view of Major, Michalak, and Valenzuela as applied to claims 77 above, and further in view of De Wilde et al. (U.S. 5,928,902), U.S. 4,722,840 (the 840 patent- of record in the November 2003 IDS), and Mountford et al (PNAS 91: 4303-07). These claims are drawn to nucleic acids encoding both an HBV S protein, and a chimeric S protein/HCV E2 protein as previously described. The teachings of the Jacobs, Major, Michalak, and Valenzuela references have been described previously. While these references

teach nucleic acids encoding the fusion protein for the formation of recombinant HBsAg particles, they do not teach the formation from nucleic acids encoding both the S protein and the chimeric protein.

The 840 patent teaches that chimeric HBsAg proteins may be expressed in mammalian cells (Columns 3 and 6), and that particles formed from such hybrid proteins may comprise either only the hybrid proteins, or the hybrid proteins in combination with other proteins (abstract). De Wilde demonstrates that hybrid particles form between the hybrid HBsAg proteins and native HBsAg protein. Column 4. The reference teaches that such particles are formed when host cells are co-transformed with nucleic acids encoding both the native and the hybrid HBsAg proteins. Id. Thus, these references teach that particles comprising both the native HBsAg and the hybrid HBsAg are, at least, functional equivalents to the particles of Jacobs (comprising only the hybrid proteins), and that they are formed in cells transfected with genes encoding each of the two proteins. However, the references do not teach the use of a single vector encoding both proteins.

The Mountford reference teaches expression vectors for the expression of two proteins in host cells. Page 4303. The reference teaches the use of a viral IRES to induce the expression of a two proteins in the same transformation vector. Id. While in this reference the authors relate the expression of two reporter genes, other art indicates that those of ordinary skill in the art would have known that such vectors could be used for the expression of other combinations of proteins. See e.g., Martínez-Salas, Curr Opin Biotechnol 10: 458-64 (esp. page 461); Pizzato et al., Gene Therapy 5: 1003-07, esp. pages 1003-04 (teaching that the first protein is expressed from a normal promoter, and the second from the viral IRES). From these teachings, it would have been

obvious to those in the art to use such a combined vector for the expression of both the native and the hybrid genes required for the production of the hybrid particles suggested by the previously cited references in combination with the 840 patent and De Wilde. Thus, the combined teaches suggest the use of hybrid particles comprising both a HBsAg and a chimeric HBsAg fused to an HCV E2 protein, and the making of expression vectors encoding such proteins for expression in mammalian cells. From the successful expression and formation of hybrid particles in each of Jacobs, De Wilde, and the 840 patent, and the successful coexpression in Mountford, those of ordinary skill in the art would have had a reasonable expectation of success. The combined teachings of these references therefore render the claimed inventions obvious.

Conclusion

19. No claims are allowed.

20. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> U.S. 2003/0211996. This reference teaches the making of fusion HBsAg/HCV E2 proteins. See e.g., page 6, Example 1. However, the reference is not considered prior art to the present application.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

JAMES HOUSEL 1/9/06
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600